Anti-PD1 Agents:

Immunotherapy agents in the treatment of metastatic melanoma

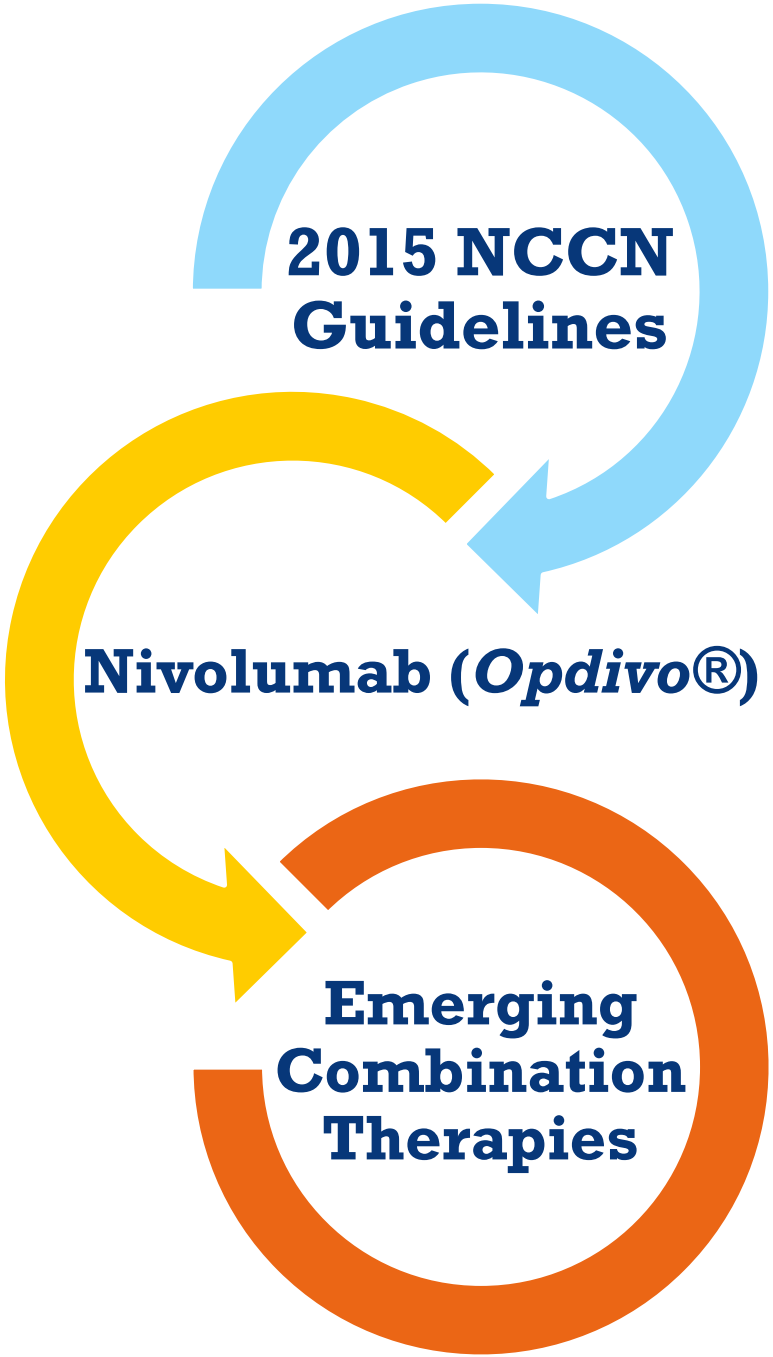
Claire Vines, 2016 Pharm.D. Candidate

Disclosure

- I have no conflicts of interest to disclose.

Objectives

- Summarize NCCN Guidelines for systemic therapies in the treatment of advanced or metastatic melanoma
- Explain the mechanism of action of immunotherapy agents, CTLA-4 and anti-PD1 agents
- List the common side effects seen with immunotherapy agents
- Summarize pivotal clinical trials for the approval and utilization of nivolumab in the treatment of advanced or metastatic melanoma


2015 NCCN Guidelines
Nivolumab (*Opdivo*®)
Emerging Combination Therapies

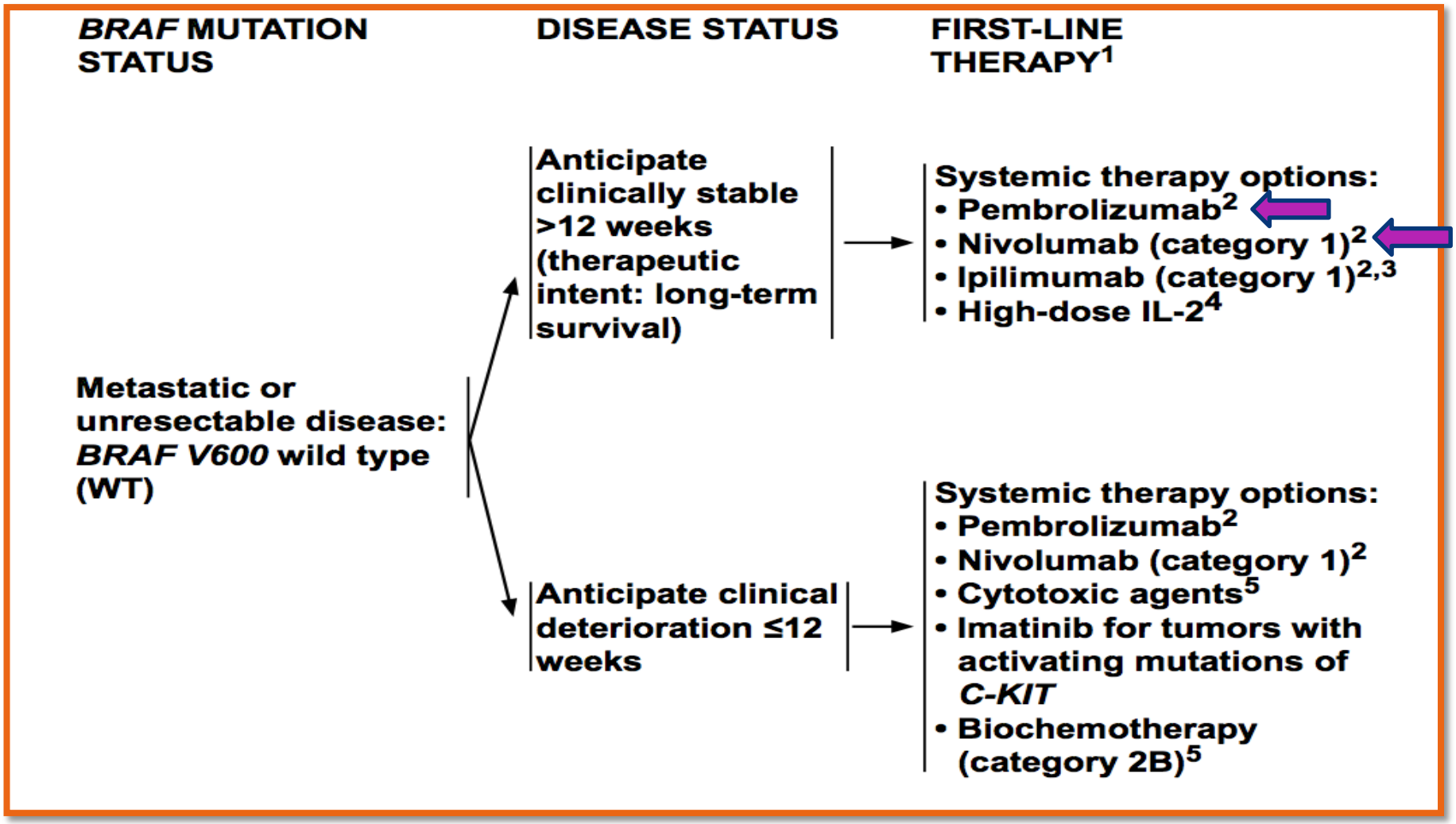
2015 NCCN Guidelines

National Comprehensive Cancer Network

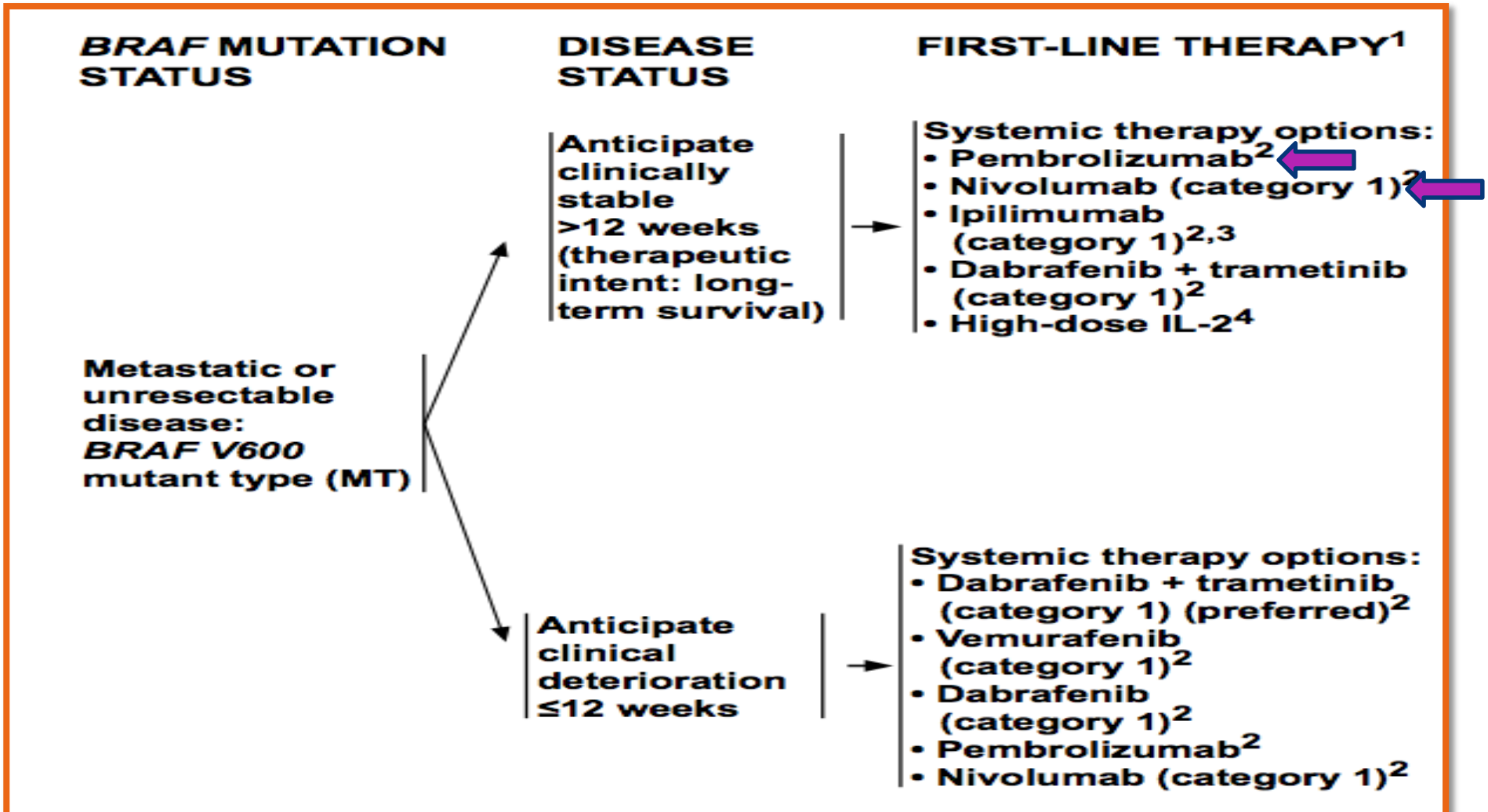
Systemic Therapy Agents

Immunotherapy	Targeted	Cytotoxic
• Ipilimumab • Pembrolizumab • Nivolumab	• Dabrafenib • Vemurafenib • Trametinib • Imatinib	• Dacarbazine • Temozolomide • Paclitaxel • Paclitaxel + carboplatin • Albumin-bound paclitaxel

Systemic Therapy for Metastatic or Unresectable Melanoma



Systemic Therapy for Metastatic or Unresectable Melanoma



Immunotherapy Agents

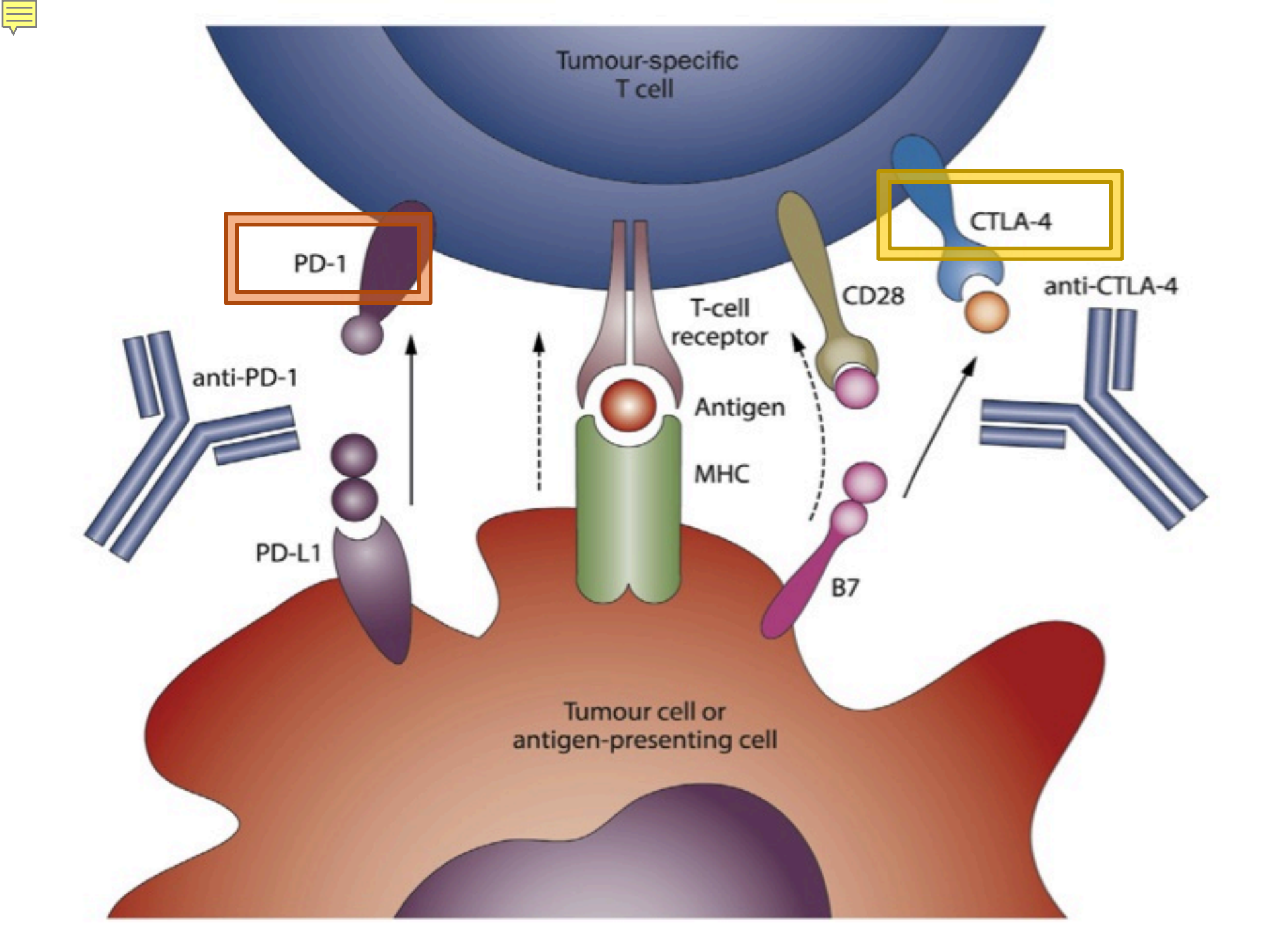
Ipilimumab (*Yervoy*®)

Pembrolizumab (*Keytruda*®)

Nivolumab (*Opdivo*®)

Immunotherapy Agents
Immune Checkpoint Inhibitors (ICIs)

- Immune system: T-cells
  - Regulated by series of co-stimulatory and inhibitory signals that serve as checkpoints
- Cytotoxic T-lymphocyte antigen-4 receptor (CTLA-4) and Programmed death-1 receptor (PD-1)
  - Checkpoint receptors that regulate immune response
  - Can be targeted and inhibited
- ICIs indirectly enhance immunological response to neoplastic cells


Tumour-specific
T cell
PD-1
CTLA-4
CD28
anti-CTLA-4
T-cell
receptor
anti-PD-1
Antigen
MHC
PD-L1
B7
Tumour cell or
antigen-presenting cell

Immune Checkpoint Inhibitors

Immune Related Adverse Events (irAEs)

- Rash and mucosal irritation
- Diarrhea or colitis
- Hepatotoxicity: elevated levels of AST and ALT
- Endocrinopathies
  - Hypophysitis, autoimmune thyroid disease, adrenal insufficiency
- Eye, kidney, pancreas, neurologic, lung, and hematologic
- Severity of observed irAE is determined by a Grade system
  - Grade 1: Mild
  - Grade 2: Moderate
  - Grade 3 or 4: Severe or life-threatening

Nivolumab

- Human IgG4 monoclonal antibody that inhibits PD1 receptors
- FDA approved December 2014 for patients with unresectable or metastatic melanoma
  - Disease progression following ipilimumab treatment or a BRAF inhibitor if BRAF V600 mutation positive
  - 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity
  - Infuse over 60 minutes, D_5W or NS
  - $1151, $2877 *(LexiComp®)*
- *CheckMate-037, CheckMate-066*

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation *CheckMate-066*

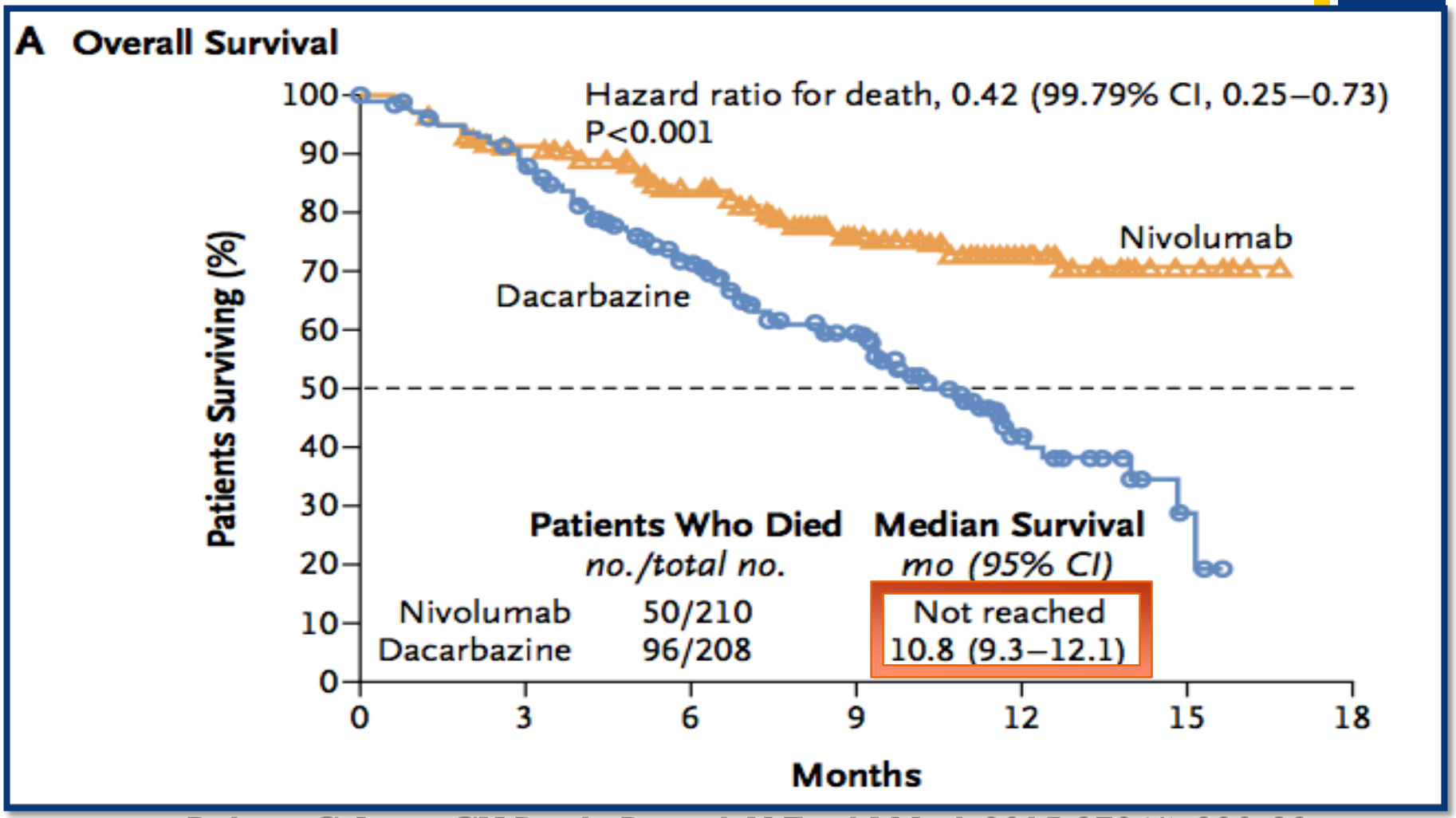
- Phase III, randomized, placebo-controlled trial
- Untreated, unresectable, Stage III or IV BRAF wild-type melanoma
- Randomized 1:1 (n=418)
  - Nivolumab 3 mg/kg IV every 2 weeks (n=210)
  - Dacarbazine (DTIC) 1000 mg/m^2 IV every 3 weeks* (n=208)
- Primary endpoint: overall survival
- Secondary endpoints: investigator-assessed progression free survival, objective response rate, PD-L1 expression

***DTIC dose is higher than recommended (LexiComp®)**

Robert C, Long GV, Brady B, et al. N Engl J Med. 2015;372(4):320-30.

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

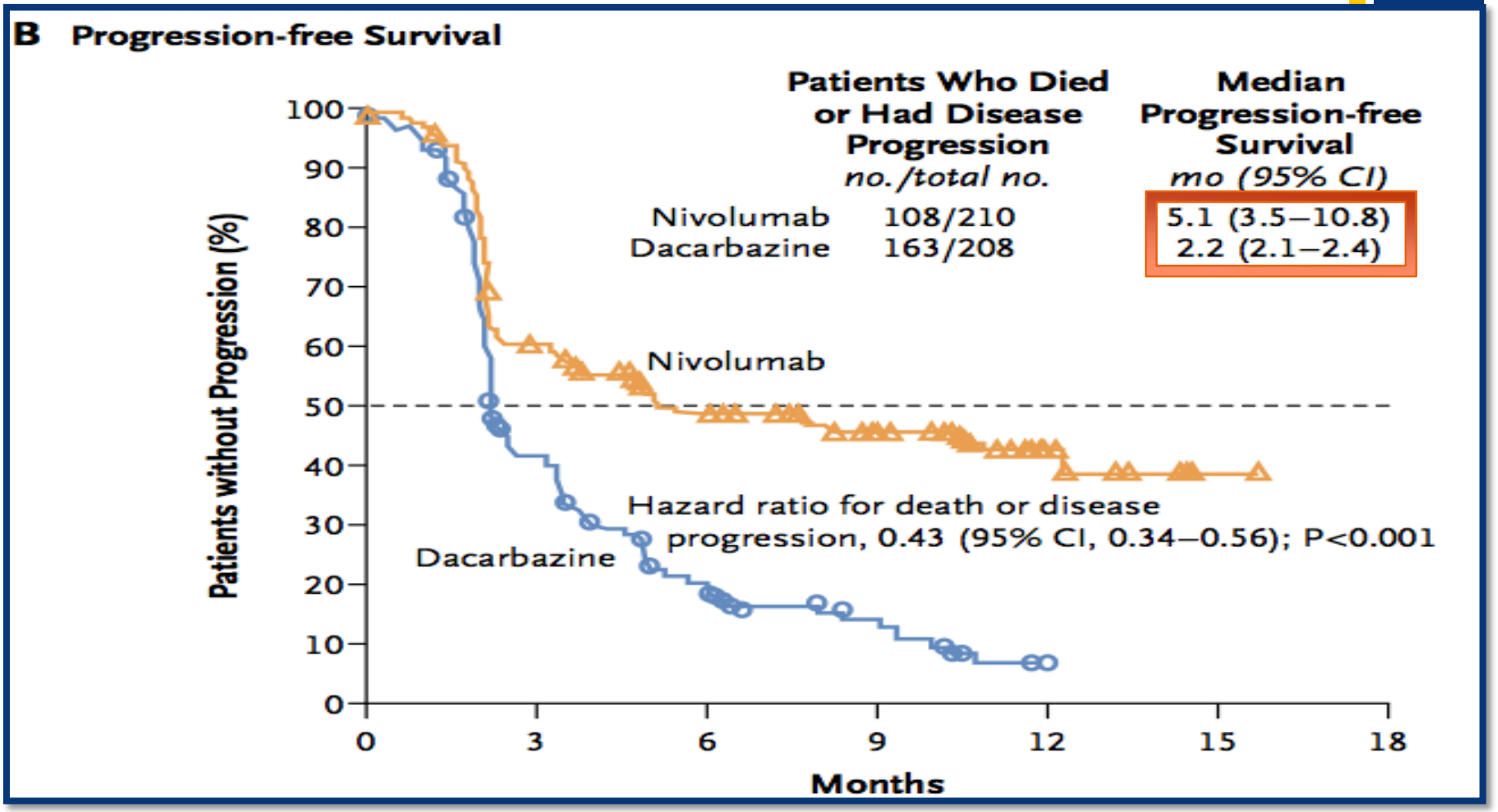
CheckMate-066



Robert C, Long GV, Brady B, et al. N Engl J Med. 2015;372(4):320-30.

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

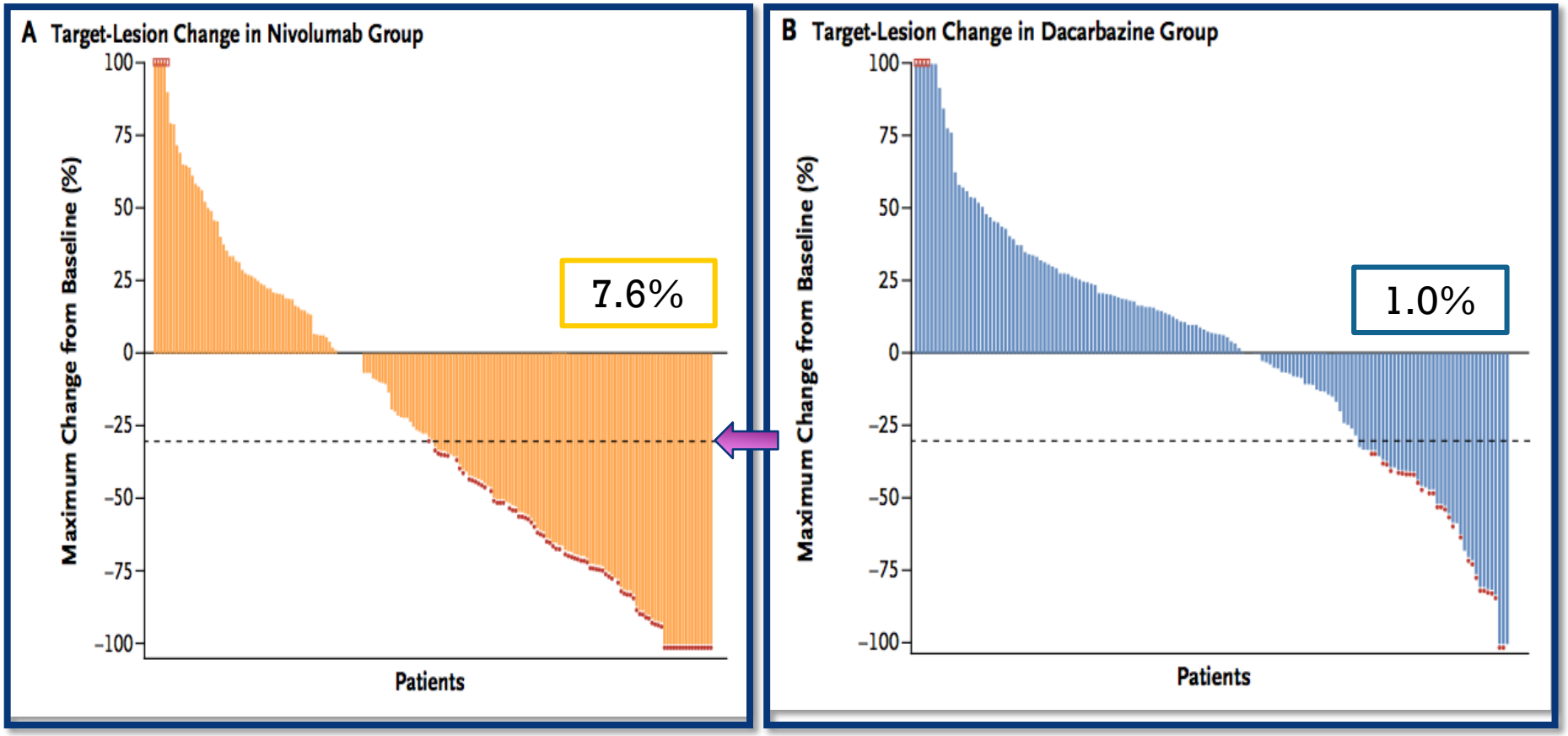
CheckMate-066



Robert C, Long GV, Brady B, et al. N Engl J Med. 2015;372(4):320-30.

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

CheckMate-066



Robert C, Long GV, Brady B, et al. N Engl J Med. 2015;372(4):320-30.

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation *CheckMate-066*

	Nivolumab	DTIC	HR (OR)	P-value
Median Overall Survival	N/A	10.8 months		
Overall Survival at 1 year (%)	72.9	42.1	0.42	<0.001
Median PFS	5.1 months	2.2 months	0.43	<0.001
ORR (%)	40.0	13.9	4.06	<0.001
Median Duration of Response	N/A	6.0 months		

Robert C, Long GV, Brady B, et al. N Engl J Med. 2015;372(4):320-30.

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

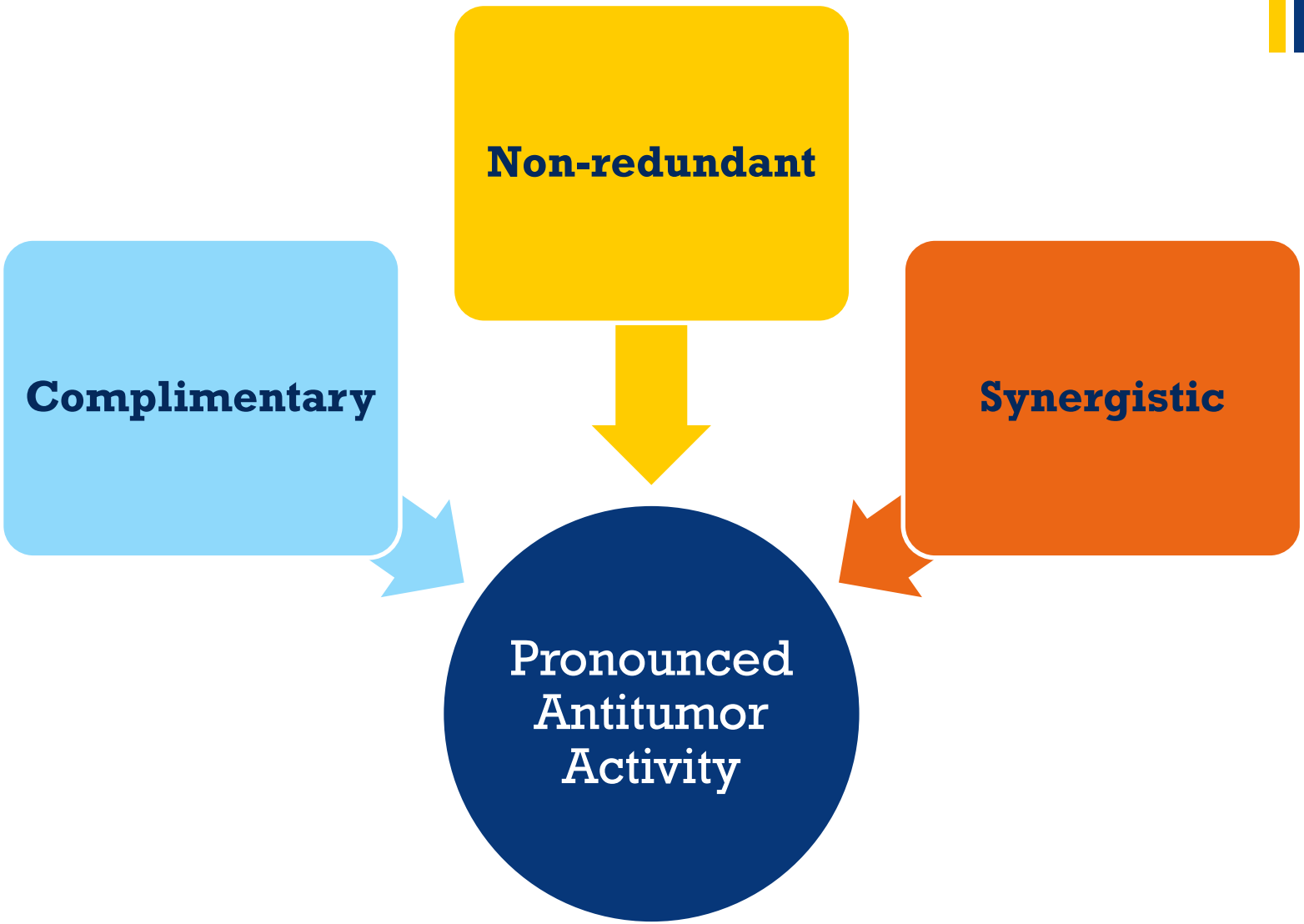
CheckMate-066

	Nivolumab	DTIC
Any adverse event (%)	74.3	75.6
Grade 3-4	11.7	17.6
Treatment discontinued	6.8	11.7
No deaths were attributed to drug toxicity		

	Nivolumab	DTIC
Most common adverse event	Fatigue, pruritus, nausea	GI and hematologic toxicities

Robert C, Long GV, Brady B, et al. N Engl J Med. 2015;372(4):320-30.

Combination Therapy:
CTLA-4 and Anti-PD1 agents



Summary

- Anti-PD1 agents
  - NCCN 2015 Guidelines: first-line therapy for metastatic melanoma
  - Panel consensus: higher response rates and less toxicities versus ipilimumab
- Combination therapy: potential advantage for durability of response
  - Rapid response of greater magnitude
  - Elevated LDH level, M1c disease, and bulky, multifocal tumor burden
  - Effect on overall survival remains to be defined
- Emerging indications
  - PD-L1 tumor expression guidance
  - Non-small cell lung cancer
  - Ovarian, metastatic Renal Cell Carcinoma, and classical Hodgkin's Lymphoma

Questions?

References

- Barbee MS, Ogunniyi A, Horvat TZ, Dang TO. Current Status and Future Directions of the Immune Checkpoint Inhibitors Ipilimumab, Pembrolizumab, and Nivolumab in Oncology. Ann Pharmacother. 2015;
- Coit, et al. Melanoma: NCCN Guidelines in Oncology (version 3.2015). www.nccn.org. Accessed June 2015.
- Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
- Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320-30.

References

- SEER Stat Fact Sheet: Melanoma of the Skin. http://seer.cancer.gov/statfacts/html/melan.html. Accessed June 20, 2015.

- Weber J, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015; 16: 375-84.

- Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013;369(2):122-33.